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Health Effects Assessment for Chlorobenzene

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with chlorobenzene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Chlorinated Benzenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-028. NTIS PB 81-117392.

U.S. EPA. 1982a. Hazard Profile for Chlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste, Washington, DC. EPA 600/8-84-015F. NTIS PB 85-15033.

U.S. EPA. 1985a. Health Assessment Document for Chlorinated Benzenes. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-015F. NTIS PB 85-150332.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The liver and kidneys appear to be target organs for chlorobenzene toxicity. Three separate subchronic oral exposure studies (one using dogs, two using rats) define comparable NOELs. The observed adverse effects indicated a higher sensitivity of the dog to chlorobenzene than the rat. Based on these findings, the highest experimental NOEL of 27.3 mg/kg/day from the dog study (Monsanto Company, 1967a) was considered appropriate to derive an RfD_{SO} and RfD_{O}. The estimated RfD_{SO} is 14 mg/day, estimated by applying an uncertainty factor of 100 (10 to extrapolate from animals to human and another factor of 10 to account for human variability) and a conversion factor of 5/7 (to adjust for partial weekly exposure). The RfD_{O} of 1.4 mg/day was derived by applying an uncertainty factor of 1000 (10 to extrapolate from subchronic to chronic exposure, 10 to extrapolate from animals to human and 10 to account for human variability) and a conversion factor of 5/7 (to account for partial weekly exposure) to the dog experimental NOEL of 27.3 mg/kg/day. This chronic oral RfD value was verified by the U.S. EPA RfD Workgroup on 01/19/89. A CS of 8 was calculated for the low blood sugar levels, vomiting, diarrhea and conjunctivitis observed in dogs at 55 mg/kg/day.

Subchronic inhalation data from several species are available, but chronic inhalation exposure assessments for chlorobenzene are lacking. An RfD_{SI} for inhalation exposure of 3 mg/day has been estimated for interim purposes, based upon the lowest subchronic LOAEL (75 ppm) reported in rats (Dilley, 1977). An interim RfD_{I} of 0.3 mg/day was estimated by applying an additional safety factor of 10 to extrapolate from subchronic to chronic exposure.

Chlorobenzene is placed in EPA Group D, i.e., not classifiable as to human carcinogenicity based on the inadequate carcinogenic evidence in experimental animals and lack of data on epidemiological studies.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
GGTP	γ-Glutamyl transpeptidase
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Chronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
SAP	Serum alkaline phosphatase
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of chlorobenzene (CAS No. 108-90-7) are as follows:

Chemical class:	monocyclic aromatic (purgeable aromatic)
Molecular weight:	112.56
Vapor pressure:	11.7 mm Hg at 20°C (Mabey et al., 1981)
Water solubility:	466.3 mg/L at 20°C (Horvath, 1982)
K_{ow}:	692 (Hansch and Leo, 1985)
Soil mobility (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%):	1.9 (Wilson et al., 1981)
K_{oc}:	126 (Sabljic, 1984)
BCF:	45.7 [Rainbow trout (muscle); Salmo gairdneri] (Branson, 1978)
	446.7 (Fathead minnow; Pimephales promelas) (Veith et al., 1979)
Half-lives in Air:	~9 days (Singh et al., 1981)
Water:	0.3 days in river (estimated) (Zoeteman et al., 1980)

Chlorobenzene has low solubility in water (Horvath, 1982). Despite the low vapor pressure, chlorobenzene is expected to evaporate quickly from water as a result of high activity coefficients in water (U.S. EPA, 1985a). Biodegradation may also occur during warmer weather and will proceed more rapidly in freshwater than in estuarine or marine ecosystems (NLM, 1987). A moderate amount of adsorption to suspended solids and sediments is expected (U.S. EPA, 1985a).

The half-life of chlorobenzene in soil could not be located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface (Wilson et al., 1981). The half-life for evaporation from soil should be longer than its evaporation half-life in water. In subsurface soil, chlorobenzene biodegrades very slowly or not at all. This compound is adsorbed moderately onto organic soil; if retained long enough, it may biodegrade. If soil is sandy or low in organic content, chlorobenzene will be relatively mobile and is expected to percolate into groundwater (NLM, 1987).

In the atmosphere, reaction with photochemically generated hydroxyl radicals is expected to be the predominant removal mechanism (Singh et al., 1981; NLM, 1987). Reaction in polluted air containing NO_x should be somewhat faster than in clean air (NLM, 1987). Global distribution of chlorobenzene in air has been suggested because chlorobenzene may be transported long distances from its emission sources (U.S. EPA, 1985a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative studies regarding absorption of chlorobenzene in humans or laboratory animals following ingestion were not located in the available literature. Reports of toxic effects in humans following ingestion or inhalation (Reich, 1934; Rosenbaum et al., 1947; Tarkhova, 1965) indicated absorption by these routes. Deichmann (1981) reported that chlorobenzene absorption from the gastrointestinal tract was facilitated by ingestion of fats and oils. Studies of the metabolism of chlorobenzene in several mammalian species indicated that absorption from the gastrointestinal tract occurred readily (Williams, 1959).

2.2. INHALATION

No quantitative studies regarding absorption in humans or experimental animals following inhalation exposure to chlorobenzene could be located in the available literature. Deichmann (1981) stated that chlorobenzene was absorbed rapidly from the lungs. No supporting data accompanied this statement.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. No reports of subchronic oral exposure of humans to chlorobenzene could be located in the available literature. Table 3-1 summarizes pertinent subchronic oral exposure data in laboratory animals. Most of these data were taken from summaries provided by U.S. EPA (1980a, 1985a) and NTP (1985). The studies reviewed by these authors seem to define similar NOELs: Monsanto Company (1967a) found no effects in dogs exposed by capsule to 27.3 mg/kg/day. Following dietary exposure for 93-99 days, no effects were reported in rats at 50 mg/kg/day (Monsanto Company, 1967b), although slightly and inconstantly elevated liver and kidney weights were reported at this level in the published version of this study (Knapp et al., 1971). Irish (1963) found no effects in rats given 14.4-18.8 mg/kg/day, 5 days/week for 192 days.

A study by Varshavskaya (1967) described CNS, liver, hematopoietic and endocrine effects in groups of seven male rats exposed to 0.01 and 0.1 mg chlorobenzene/kg/day by gavage. The U.S. EPA (1980a) considered the results of Varshavskaya (1967) to be questionable primarily because these data suggested effects at dosages far lower than those indicated by other investigators (see Table 3-1). Also, data generated by Hollingsworth et al. (1956) in a similar study of the toxicity of o-dichlorobenzene indicated similar effects, but were associated with dosages >3 orders of magnitude greater than those reported by Varshavskaya (1967).

The NTP (1985) conducted range-finding studies in which groups of 10/sex F344/N rats and 10/sex B6C3F1 mice were treated with 0, 60, 125, 250, 500 or 750 mg/kg chlorobenzene by gavage on 5 days/week for 13 weeks. The dosages were 0, 42.9, 89.3, 178.6, 357 and 538 mg/kg/day, respectively, when

TABLE 3-1

Subchronic Oral Toxicity of Chlorobenzene in Experimental Animals

Species	Dose (mg/kg/day)	Duration (days)	Effects	Reference
Dogs (4M,4F)	27.3	90	None	Monsanto Company, 1967a; Knapp et al., 1971
	54.6	90	Diarrhea and vomiting; conjunctivitis	
	272.5	90	Mortality 4/8 in 3-5 weeks; increased immature leukocytes, SGOT, bilirubin, cholesterol; decreased blood sugar; histopathological changes in liver, kidneys, spleen	
Rats	12.5 or 50	93-99	None	Monsanto Company, 1967b
	100	93-99	Increased liver and kidney weights	
	250	93-99	Increased liver and kidney weights; retarded growth in males	
Rats	14.4-18.8	192	None	Irish, 1963
	144	192	Increased liver, kidney weights, salivation; some histopathological changes in liver; partial alopecia	
	288 (treated 5 days/week)	192	Increased liver, kidney weights, salivation; some histopathological changes in liver; partial alopecia	
Rats	12.5	93-99	None	Knapp et al., 1971
	50	93-99	Increased liver and kidney weights	

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TABLE 3-1 (cont.)

Species	Dose (mg/kg/day)	Duration (days)	Effects	Reference
Rats	250	93-99	Increased liver and kidney weights, retarded growth in males	Knapp et al., 1971
Mouse	42.9	13 weeks	1/10 males with hepatic necrosis	NTP, 1985
	89.3	13 weeks	Increased liver weights in males; 1/10 males with hepatic necrosis	
	178.6	13 weeks	>50% reduction in weight gain, increased excretion of coproporphyrins in females, increased liver weights, lesions of the liver, kidney, bone marrow, spleen and thymus	
	357	13 weeks	100% lethal to males within 1 week, reduced body weight gains, polyuria in females, increased liver weights, lesions of the liver, kidney, bone marrow, spleen and thymus	
	538	10 weeks	100% lethal to males within 1 week and to female mice within 10 weeks, lesions of the liver, kidney, bone marrow, spleen and thymus at death	
Rat	42.9	13 weeks	None	NTP, 1985
	89.3	13 weeks	None	
	178.6	13 weeks	Minimal centrolobular hepatocellular necrosis	

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TABLE 3-1 (cont.)

Species	Dose (mg/kg/day)	Duration (days)	Effects	Reference
Rat	357	13 weeks	Decreased body weight gain, increased GGTP and alkaline phosphatase in females, increased excretion of porphyrins, centrolobular hepatocellular necrosis, nephropathy in males, myeloid depletion of bone marrow	NTP, 1985
	538	13 weeks	Decreased body weight gain and survival of animals, hematologic effects, increased GGTP and alkaline phosphatase in females, polyuria in males, increased excretion of porphyrins, centrolobular hepatocellular necrosis, nephropathy, lymphoid depletion of thymus and spleen, myeloid depletion of bone marrow	

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adjusted for the intermittent exposure (5 days/week). Body weight, urinalysis indices, hematology indices, clinical chemistry indices, organ weights and histology of numerous tissues were evaluated in all animals. Treatment-related effects were not observed at 42.9 or 89.3 mg/kg/day in rats; however, at 42.9 mg/kg/day one male mouse developed hepatic necrosis, and at 89.3 mg/kg/day male mice had increased liver weight and one male mouse also had symptoms of hepatic necrosis (see Table 3-1).

Effects in the rats included decreased survival and lymphoid depletions of the thymus and spleen at 538 mg/kg/day, and decreased body weight gain, nephropathy, myeloid depletion of the bone marrow, and scattered alterations in urinary and clinical chemistry, hematology, organ weight and porphyrin metabolism at ≥357 mg/kg/day (NTP, 1985). Dose-dependent hepatocellular necrosis occurred at ≥178.6 mg/kg.

In mice, decreased body weight gain, survival, dose-dependent hepatocellular necrosis, nephropathy, thymic necrosis and lymphoid or myeloid depletion of the thymus, spleen and bone marrow occurred at ≥178.6 mg/kg. In conclusion, the results of the 13-week studies largely corroborate the earlier reports that chlorobenzene exposure can adversely affect the liver, kidneys and hematopoietic system. Male mice appeared to be affected more severely than females in the 13-week study conducted by NTP (1985).

3.1.2. Inhalation. No studies regarding subchronic inhalation exposure of humans to chlorobenzene could be located in the available literature. Because of the potential for occupational exposure being long-term, these reports are discussed in Section 3.2.2.

Several studies of subchronic inhalation exposure of laboratory animals to chlorobenzene have been reviewed by Deichmann (1981) and U.S. EPA (1985a) and are summarized in Table 3-2. Dilley (1977) demonstrated small, focal

TABLE 3-2

Subchronic Inhalation Toxicity of Chlorobenzene in Experimental Animals

Species	Exposure	Dose[a] (mg/kg/day)	Duration (days)	Effects	Reference
Rats	200 ppm, 7 hours/day, 5 days/week	122	44	None	Irish, 1963
	475 and 1000 ppm, 7 hours/day, 5 days/week	290 and 611	44	Increasing severity of hepatocegaly, histopathological changes	
Rats	0.75, 1.50 or 2 mg/l 6 hours/day, 5 days/week	85, 171 or 228	87	None	Monsanto Company, 1978
Rats	0.1 or 1.0 mg/m³ continuous	0.06 or 0.6	72-80	Liver necrosis and regeneration; kidney hyperplasia, encephalopathy, pneumonia	Khanin, 1977
Rats	0.1 mg/m³ continuous	0.06	60	None	Tarkhova, 1965
	1.0 mg/m³ continuous	0.6	60	Inhibited chronaxia of antagonistic muscles at 39 days; increased blood cholinesterase	
Rats	0.1, 1.25 or 1.5 mg/l[b]	ND	49-98	Chronaximetric inhibition	Pislaru, 1960
Rats	0.1 mg/l, 3 hours/day every other day	4	259	Inhibition of extensor tibialis at 7-14 weeks, normal by 20 weeks	Gabor and Raucher, 1960
Rats	75 or 250 ppm 7 hours/day, 5 days/week	46 or 153	120	Focal lesions in adrenal cortex and and kidney tubules; congestion of liver and kidney, decreased SGOT	Billey, 1977
Rabbits	75 or 250 ppm, 7 hours/day, 5 days/week	38 or 126	120	Decreased SGOT	Billey, 1977
Rabbits	200 ppm, 7 hours/day, 5 days/week	101	44	None	Irish, 1963
Guinea pigs	200 ppm, 7 hours/day, 5 days/week	91	44	None	Irish, 1963

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TABLE 3-2 (cont.)

Species	Exposure	Dose[a] (mg/kg/day)	Duration (days)	Effects	Reference
Dogs	0.75 mg/l, 6 hours/day, 5 days/week	45	87	None	Monsanto Company, 1978
	1.50 mg/l, 6 hours/day, 5 days/week	91	87	Weight loss, conjunctivitis, moribund by 31 days	
	200 mg/l, 6 hours/day, 5 days/week	12,092	87	Weight loss, hypoactivity and conjunctivitis; vacuolated hepatocytes, cytoplasmic vacuolation of renal tubules, bilateral atrophy of seminiferous tubules; leukocytopoenia; elevated SAP, SGOT, SGPT; aplastic bone marrow, mortality in 5/8 dogs by 25-29 days	

[a]Dose in mg/kg was calculated assuming the following inhalation rates and body weights: rats - 0.223 m³/day and 0.35 kg; rabbits - 2.0 m³/day, 3.8 kg; guinea pigs - 0.4 m³/day, 0.84 kg; dogs - 4.3 m³/day, 12.7 kg (U.S. EPA, 1986a)

[b]Exposure data insufficient for calculation of dose

ND - Not derived because exposure data are insufficient

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lesions in the adrenal cortex and kidney tubules and decreased SGOT in rats exposed to 75 ppm chlorobenzene 7 hours/day, 5 days/week for 120 days. This dosage, which corresponds to an intake of 46 mg/kg/day, defined a LOAEL in rats from inhalation exposure to chlorobenzene. In an earlier study, no effects were seen in rats exposed to 122 mg/kg bw/day for 44 days (Irish, 1963).

Several reports from the foreign literature indicate effects in rats at exposures leading to dosages far below those associated with no effects in reports from the domestic literature. For example, Khanin (1977) reported histopathological lesions in several organs at 0.06 mg/kg bw/day. Neuromuscular dysfunction was reported in rats at exposures leading to dosages of 0.06-4 mg/kg bw/day (Tarkhova, 1965; Pislaru, 1960; Gabor and Raucher, 1960). In the absence of additional corroborating evidence from other laboratories, the data are not considered reliable for use in risk assessment.

In subchronic inhalation experiments in other species, no adverse effects were observed in rabbits at 38-126 mg/kg bw/day (Dilley, 1977; Irish, 1963), in guinea pigs at 91 mg/kg bw/day (Irish, 1963) or in dogs at 45 mg/kg bw/day (Monsanto Company, 1978). Dogs appear to be the most sensitive species tested, however, as weight loss and moribundity occurred in this species by 31 days of exposure to 91 mg/kg bw/day (Monsanto Company, 1978).

3.2. CHRONIC

3.2.1. Oral. No reports of chronic oral exposure of humans to chlorobenzene were located in the available literature. An NTP (1985) carcinogenicity bioassay was conducted in which groups of 50 F344/N rats/sex and 50 female B6C3F1 mice were treated with chlorobenzene in corn oil by gavage at doses of 0, 60 or 120 mg/kg on 5 days/week for 103 weeks. Groups of 50 male B6C3F1 mice were treated similarly at doses of 0, 30 or 60 mg/kg.

Both untreated and vehicle-treated controls were maintained. Statistically significant reduced survival occurred in the low- and high-dose male mice (56% and 58% at the end of the study, respectively, vs. 78% in the vehicle controls) and high-dose male rats (52% vs. 78%), but there were no treatment-related clinical signs of toxicity, decreases in body weight gain or nonneoplastic lesions. Treated rats showed "equivocal evidence for mild chlorobenzene-induced hepatocellular necrosis" that was not considered to be clear evidence of hepatotoxicity. Neoplastic nodules, but not tumors, occurred at a significantly increased incidence in the high-dose male rats (Section 4.2.), but this was not suggested as a cause of the reduced survival.

3.2.2. Inhalation. The only available reports of chronic human exposure to chlorobenzene were summaries by U.S. EPA (1985a) from which this discussion was adapted. Girard et al. (1969) reported the case of a 70-year-old woman exposed for 6 years to a glue containing 70% chlorobenzene. From the time she began using the glue, she experienced headaches and irritation of the mucosa of the upper respiratory tract and eyes. After 6 years, she had developed medullary aplasia. Exposure was not quantified.

Rosenbaum et al. (1947) examined 28 factory workers, many of whom complained of headaches and showed signs of somnolescence and dyspepsia. Other complaints included tingling, numbness and stiffness of the extremities (8 workers), hyperesthesia of the hands (4 workers), and spastic contractions of the finger muscles (9 workers) or of the gastrocnemius (2 workers). These workers had reportedly been exposed for 1-2 years, but details of exposure were not specified. No neurotoxic signs were displayed by 26 workers exposed to chlorobenzene alone or combination of benzene and chlorobenzene for <1 year.

No reports of chronic inhalation exposure of laboratory animals to chlorobenzene could be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Groups of 32-33 pregnant Fischer 344 rats and 30 pregnant New Zealand White rabbits were exposed to 0, 75, 210 or 590 ppm of 99.982% pure chlorobenzene by inhalation for 6 hours/day on days 6-15 (rats) or 6-18 (rabbits) of gestation (John et al., 1984). Standard teratologic evaluations, including soft tissue and skeletal examinations, were conducted on gestation day 21 in the rats and gestation day 29 in the rabbits.

Maternal toxicity, evidenced by decreased body weight gain on gestation days 6-8 and increased absolute and relative liver weights, occurred in the rats exposed to 590 ppm (John et al., 1984). Delayed ossification of fetal vertebral centra and bilobed thoracic centra, which was reportedly indicative of a slight delay in skeletal development and apparently related to the maternal toxicity, also occurred in offsprings of rats exposed to 590 ppm. Treatment-related embryotoxic or teratogenic effects were not observed in the rats at any exposure concentration.

There was evidence of slight maternal toxicity among rabbits exposed to 210 or 590 ppm, as absolute and relative liver weights were increased in these groups (John et al., 1984). Several cases of external and visceral malformations (head and facial anomalies, heart defects) occurred among the exposed groups, but the effects were not dose-related and affected fetuses did not all show the same malformations. To ascertain whether the low incidence of malformations was a true effect of treatment, a second inhalation study was conducted in which groups of 30-32 pregnant rabbits were exposed to 0, 10, 30, 75 or 590 ppm chlorobenzene (other aspects of the experimental design were the same as those in the first study). This study did not reveal any significant increase or trend for clustering of malformations in

the exposed groups when considered individually or collectively. Maternal toxicity, as in the first study, was evidenced by significantly increased liver weights occurring at 210 and 590 ppm. There were no treatment-related embryotoxic effects.

In a two-generation reproduction study, groups of 30 male and 30 female Sprague-Dawley rats (designated as F_0) were exposed to chlorobenzene vapor at concentrations of 0, 50, 150 or 450 ppm for 10 weeks prior to mating and during mating, gestation and lactation. The progeny of the F_0 generation (designated as F_1) was exposed to the same concentration of chlorobenzene (30 males and 30 females/group) 1 week postweaning for 11 weeks prior to mating and through mating, gestation and lactation. No adverse effects on reproductive performance or fertility were observed in this two-generation study. The only significant histopathological changes observed were hepatocellular hypertrophy and renal changes in the F_0 and F_1 male rats at 150 and 450 ppm.

3.4. TOXICANT INTERACTIONS

No pertinent data that confirmed the interaction of chlorobenzene with other xenobiotics could be located in the available literature. Generalizing that the halogenated benzenes appeared to increase the activity of microsomal cytochrome P-450-dependent enzyme systems, the U.S. EPA (1980a) suggested that exposure to chlorobenzene might be expected to hasten metabolism of other xenobiotics to either more or less toxic metabolites.

Shelton and Weber (1981) investigated the hepatotoxicity of a mixture of carbon tetrachloride and chlorobenzene (1:38 molar ratio, mixed in corn oil) in male CF-1 mice. The dosages used (0.01 mL/g bw) were given by intraperitoneal injection. Although parameters of hepatotoxicity were not mentioned, the U.S. EPA (1985a) stated that the dose-response did not deviate from that predicted on the basis of concentration addition.

4. CARCINOGENICITY

4.1. HUMAN DATA

No reports that associated chlorobenzene with cancer in humans could be located in the available literature.

4.2. BIOASSAYS

The NTP (1985) conducted a study of the carcinogenicity of chlorobenzene in F344/N rats and B6C3F1 mice. Based on data from a 13-week dose range-finding experiment (see Section 3.1.1.), 50 rats/sex were treated by gavage with 60 or 120 mg/kg, 5 days/week for 103 weeks. Both untreated and vehicle-treated control groups of 50 rats/sex were maintained.

Throughout the study, body weight of treated and control rats remained comparable (NTP, 1985). Survival rates were similar until ~70 weeks of treatment, at which time survival in high-dose group males was significantly reduced. Survival at the end of 2 years was 68, 78, 64 and 52% in untreated control, vehicle-treated control, low-dose and high-dose males, respectively. Among female rats, 2-year survival data were 74, 58, 60 and 62% in untreated control, vehicle-treated control, low-dose and high-dose groups, respectively.

In male rats, a significant increase in neoplastic nodules in the liver was observed in the high-dose group (Table 4-1) as determined by both the incidental tumor test ($p=0.021$) and the Cochran-Armitage test for dose-related trend ($p=0.027$). Liver carcinomas in male rats were found only in the vehicle-treated group (2/50). Combining the incidences of neoplastic nodules and carcinomas failed to create an overall tumor incidence that was statistically significant. There was no evidence of neoplastic nodule or liver tumor formation in female rats.

TABLE 4-1

Statistical Comparisons of Liver Tumors in Male Rats
Treated with Chlorobenzene*

Tumor Type	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Neoplastic nodule	4/50 (8%)	2/50 (4%)	4/49 (8%)	8/49 (16%)
Incidental tumor test		p=0.011	p=0.290	p=0.021
Cochran-Armitage test		p=0.027	NA	NA
Fisher exact test		NA	p=0.329	p=0.043
Carcinoma	0/50 (0%)	2/50 (4%)	0/49 (0%)	0/49 (0%)
Incidental tumor test		p=0.139	p=0.283	p=0.331
Cochran-Armitage test		p=0.098	NA	NA
Fisher exact test		NA	p=0.253	p=0.253
Neoplastic nodule or carcinoma	4/50 (8%)	4/50 (8%)	4/49 (8%)	8/49 (16%)
Incidental tumor test		p=0.054	p=0.570	p=0.083
Cochran-Armitage test		p=0.121	NA	NA
Fisher exact test		NA	p=0.631	p=0.168

*Source: NTP, 1985

NA = Not applicable

Pituitary adenomas in the high-dose males and females and endometrial stromal polyps in the low-dose females occurred at incidences that were significantly lower than in the controls.

The carcinogenicity of chlorobenzene was also tested in B6C3F1 mice (NTP, 1985). Males were treated with 30 or 60 mg/kg and females were treated with 60 or 120 mg/kg, 5 days/week for the 2-year (103-week) treatment period. Survival in the low- and high-dose males was marginally less than in the controls. The dosages were chosen on the basis of a preliminary 13-week dose range-finding study. It appeared that the doses chosen for the chronic bioassay, based on the data generated by the 13-week preliminary study, were too low, and that the maximum tolerated dose had not been approached (U.S. EPA, 1985a). No tumors occurred with frequencies that differed significantly from those in the control groups.

The U.S. EPA (1985a) stated that the data generated by these studies were not sufficient to draw conclusions about the carcinogenicity of chlorobenzene.

4.3. OTHER RELEVANT DATA

Studies of the mutagenicity of chlorobenzene in microorganisms have yielded mixed results, with positive results observed only in tests with Saccharomyces cerevisiae (Simmon et al., 1979) and Streptomyces antibioticus (Keskinova, 1968) (Table 4-2).

In a sex-linked recessive lethal test in Drosophila melanogaster (Bioassay Systems Corp., 1982), male flies were exposed to 36,000 or 128,400 ppm of chlorobenzene for 1 hour. The exposed flies were mated at 1-3 days (to sample effects on spermatozoa), 4-5 days (to sample effects on spermatids) and 6-7 days (to measure effects on spermatocytes) after exposure. No evidence of mutagenicity was found in 11,543 chromosomes from treated flies compared with 9430 chromosomes from control flies.

TABLE 4-2

Mutagenicity Testing of Chlorobenzene

Test System	Metabolic Activation	Concentration	Result	Reference
Aspergillus nidulans	-	200 µg/mL	negative	Prasad, 1970
Salmonella strains TA1535, TA1537, TA1538, TA92, TA98, TA100	±	0.1-0.5 µL/plate	negative	Simmon et al., 1979
Salmonella typhimurium strains TA1535, TA1537, TA98, TA100	±	3.3-3333 µg/plate	negative	NTP, 1982
Salmonella typhimurium strains	±	100 µg/plate	negative	Merck and Company, 1978
Saccharomyces cerevisiae	±	0.05-6%	positive	Simmon et al., 1979
S. cerevisiae	±	0.01-5 µL/plate	negative	Monsanto Company, 1976
Escherichia coli ($polA^+/polA^-$)	-	10-20 µL/plate	negative	Simmon et al., 1979
Bacillus subtilis (rec^-/rec^+)	-	10-20 µL/plate	negative	Simmon et al., 1979
Streptomyces antibioticus	-	NR	positive	Keskinova, 1968

NR = Not reported

A positive response was obtained in a test for *in vitro* induction of chromosomal aberrations in Chinese hamster ovary cells (U.S. EPA, 1982b). Concentrations of 444, 266 and 178 µg/mL were tested in assays that did not incorporate a metabolic activating system; concentrations of 493, 296, 197 and 99 µg/mL were assayed with an S-9 activating system. A positive response was observed in the S-9 activated system after a 4-hour exposure but not after a 2-hour exposure. It is concluded in U.S. EPA (1985a) that the negative results may be due to an insufficient exposure time, and chlorobenzene is clastogenic in Chinese hamster ovary cells.

A negative response was obtained in a forward mutation test in mouse lymphoma L5178Y cells (Monsanto Company, 1976). A metabolic activating system was used at concentrations of 0.0001-0.01 µL/mL but not at 0.001-0.1 µL/mL.

4.4. WEIGHT OF EVIDENCE

No evidence of carcinogenicity associated with exposure to chlorobenzene in humans was located in the available literature. IARC has not evaluated the human risk associated with oral or inhalation exposure to chlorobenzene, and there are no conclusions about the carcinogenicity in U.S. EPA (1985a) as a result of the inadequate data base. In the NTP (1985) bioassay, chlorobenzene administration increased the occurrence of neoplastic nodules of the liver in high-dose male F344/N rats, providing evidence of carcinogenicity in male rats [as discussed in U.S. EPA's Risk Assessment Forum Report (U.S. EPA, 1986c)]. However, two liver carcinomas were observed in vehicle-treated rats but none in rats treated with chlorobenzene, and combining the incidences of benign neoplastic nodules and carcinomas does not result in an overall statistically significant tumor

increase. Carcinogenic effects of chlorobenzene were not observed in female F344/N rats or in male or female B6C3F1 mice. Therefore, although the NTP bioassay provided some, but not clear, animal evidence of carcinogenicity, the overall carcinogenic evidence in animals is judged to be inadequate.

In conclusion, because of the combination of inadequate carcinogenic evidence in experimental animals and lack of human evidence, chlorobenzene is placed in EPA Group D; i.e., not classifiable as to human carcinogenicity using the weight-of-evidence classification scheme (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

A summary of regulatory standards and criteria for chlorobenzene is presented in Table 5-1. ACGIH (1986), OSHA (1985) and NIOSH (1982) recommend a TLV-TWA of 75 ppm (350 mg/m³) for occupational exposure to chlorobenzene. No STEL has been set.

The U.S. EPA (1980a) derived an ambient water quality criterion of 488 µg/ℓ to protect human health. This criterion is based on an ADI of 1.008 mg/day; average water consumption of 2 ℓ/day and consumption of fish and shellfish are also considered.

TABLE 5-1

Current Regulatory Standards and Criteria for Chlorobenzene

Standard or Criterion	Value	Reference
TLV-TWA		
TWA	75 ppm (~350 mg/m³)	ACGIH, 1986
	75 ppm	NIOSH, 1982
Ambient water quality criteria:		
Freshwater aquatic life		
Acute toxicity	250 µg/ℓ	U.S. EPA, 1980a
Saltwater aquatic life		
Acute toxicity	160 µg/ℓ	U.S. EPA, 1980a
Chronic toxicity	129 µg/ℓ	U.S. EPA, 1980a
Ambient water quality criterion:		
Human life		
Organoleptic	488 µg/ℓ	U.S. EPA, 1980a
	20 µg/ℓ	U.S. EPA, 1980a

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). NOAELs from subchronic oral studies include 14.4 mg/kg/day in rats (Irish, 1963), 50 mg/kg/day in rats (Monsanto Company, 1967b), 89.3 mg/kg/day in rats (125 mg/kg, 5 days/week) (NTP, 198-), 12.5 mg/kg/day in rats (Knapp et al., 1971) and 27.3 mg/kg/day in dogs (Monsanto Company, 1967a; Knapp et al., 1971). The Irish (1963) study reported a NOEL of 14.4 mg/kg/day and LOAEL of 144.4 mg/kg/day; however, intermediate doses were not evaluated. The Monsanto Company (1967a,b) studies defined a NOAEL of 50 mg/kg/day and a LOAEL of 100 mg/kg/day for the rat. In contrast, a NOEL of 27.3 mg/kg/day and a LOAEL of 55 mg/kg/day were defined for the dog. The observed adverse effects indicated a higher sensitivity of the dog to chlorobenzene than the rat. Based on these findings, the highest dog NOEL of 27.3 mg/kg/day (Monsanto Company, 1967a) was considered appropriate to derive an RfD_{SO}. A conversion factor of 5/7 is used to adjust for partial weekly exposure (5 days/week) and an uncertainty factor of 100 is applied to account for interspecies extrapolation (10) and to protect especially sensitive populations (10). Assuming a body weight for man of 70 kg, an RfD_{SO} can be calculated as 0.2 mg/kg/day or 14 mg/day for a 70 kg human.

Immature leukocytes, low blood sugar, conjunctivitis, vomiting and diarrhea were reported in dogs at 55 mg/kg/day; higher doses caused mortality and histopathological lesions in liver and kidneys (Monsanto Company, 1967a). A human MED was calculated by multiplying the dog MED by the cube root of the ratio of the body weight of dogs (assumed: 12.7 kg) to that of humans (assumed: 70 kg) and dividing the result by 10, an uncertainty factor chosen to reflect the unknowns in extrapolating from a subchronic study to

chronic application. The result, 3.1 mg/kg/day, is multiplied by 70 and an MED of 218 mg/day for a 70 kg man is derived. This MED corresponds to an RV_d of 2.0; the effects of vomiting, diarrhea, conjunctivitis and immature luekocytes rate an RV_e of 4. A CS of 8, the product of RV_d and RV_e, is calculated.

6.1.2. Inhalation (RfD_{SI}). NOELs of 85-228 mg/kg/day in rats (Monsanto Company, 1978; Irish, 1963), 101 mg/kg/day in rabbits (Irish, 1963), 91 mg/kg/day in guinea pigs (Irish, 1963) and 45 mg/kg/day in dogs (Monsanto Company, 1978) were identified for subchronic inhalation exposures (see Table 3-2). NOAELs of 38 and 126 mg/kg/day, which reflect decreased SGOT levels, were identified in rabbits (Dilley, 1977) (see Table 3-2). In another experiment by Dilley (1977) (see Table 3-2), exposures at 46 mg/kg/day (75 ppm, 7 hours/day, 5 days/week for 120 days) produced small focal lesions in the adrenal cortex and kidney tubules, congestion of the liver and kidneys and decreased SGOT in rats; this intake represents a LOAEL. Dogs that received 91 mg/kg/day (1.5 mg/ℓ, 6 hours/day, 5 days/week) experienced weight loss and were moribund by 31 days (Monsanto Company, 1978). The available data indicate that dogs are more sensitive than rats or rabbits, but do not provide a NOEL (45 mg/kg/day in dogs) or NOAEL (38 mg/kg/day in rats) that is safely below the 46 mg/kg/day LOAEL in rats. The 46 mg/kg/day rat LOAEL therefore provides the most appropriate basis for an RfD_{SI}. Assuming a human body weight of 70 kg and using an uncertainty factor of 1000 to estimate a NOAEL from a LOAEL (10), for interspecies extrapolation (10), and to protect unusually sensitive human subgroups (10), the RfD_{SI} is calculated to be 3 mg/day.

The only teratogenic effects, evidenced by delayed ossification, occurred in the offspring of rats exposed to 590 ppm chlorobenzene for 6

hours/day on days 6-15 of gestation (John et al., 1984). Using the assumptions footnoted in Table 3-2 this exposure provided an intake of 433 mg/kg/day, which was well above the LOAEL used to derive the RfD_{SI}. Therefore the RfD_{SI} derived, based on minor histological changes in rats at 46 mg/kg/day, is appropriate.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). No reports of chronic oral exposure of humans to chlorobenzene were located in the available literature. In the only chronic animal study, reduced survival occurred in male mice (marginal reduction) treated by gavage at doses of 30 or 60 mg/kg, 5 days/week for <103 weeks and in male rats that were similarly treated with 120 (but not 60) mg/kg (NTP, 1985). Treatment-related clinical signs of toxicity or decreases in body weight were not observed in either species. The only indications of pathologic effects were equivocal evidence of mild hepatocellular necrosis in low- and high-dose rats of both sexes, and neoplastic nodules in the livers of high-dose male rats. NTP (1985) concluded that treatment was not a likely cause of reduced survival in the mice, and that the toxicological significance of reduced survival in the rats is unknown. A NOAEL of 60 mg/kg is identified by the chronic studies in rats and mice for the following reasons: survival in the male mice was "not adversely affected by administration of chlorobenzene" at doses of 30 and 60 mg/kg, equivocal mild hepatocellular necrosis without other effects occurred at 60 mg/kg in rats, and neoplastic nodules in the liver and reduced survival occurred at 120 mg/kg in rats.

The 60 mg/kg NOAEL, which is equivalent to 42.9 mg/kg/day when adjusted for partial weekly (5 days/7 days) exposure, is most appropriately used to

support the NOEL of 27.3 mg/kg/day in the Monsanto Company (1967a) subchronic oral study with dogs, in which dogs were more sensitive than rats (see Section 6.1.1.). Therefore, it appears that the NOEL of 27.3 mg/kg/day in the 90-day dog study is the most appropriate basis for an RfD for chronic oral exposure. Application of an uncertainty factor of 1000, a factor of 10 to estimate a chronic NOAEL from a subchronic NOAEL, 10 to extrapolate from dogs to humans, and 10 to protect unusually sensitive individuals and a conversion factor of 5/7 to account for partial weekly exposure results in an RfD_0 of 0.02 mg/kg/day or 1.4 mg/day for a 70 kg human. This value was verified by the U.S. EPA RfD Workgroup on 01/19/89. An AADI of 6 mg/day was calculated from the 125 mg/kg NOAEL identified in the NTP prechronic bioassays with rats and mice (U.S. EPA, 1985b).

6.2.2. Inhalation (RfD_I). No reports of chronic exposure of humans to chlorobenzene that were satisfactory for risk assessment or studies of chronic animal exposure could be located in the available literature. The study by Dilley (1977), which was used to derive the RfD_{SI} of 3 mg/day (see Section 6.1.2.), can be used to derive an RfD_I for inhalation exposure. An additional uncertainty factor of 10 to account for derivation of a chronic RfD_I from subchronic data results in an RfD_I of 0.3 mg/day. This RfD_I value was derived for interim purposes and the issue of inhalation RfD for chlorobenzene is pending discussion by the EPA RfD Workgroup.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. No reports of carcinogenicity in humans or animals resulting from oral exposure to chlorobenzene could be located in the available literature. In the only NTP (1985) bioassay in which chlorobenzene was administered to rats and mice by gavage, the incidence of neoplastic nodules was increased significantly in high-dose males only. Chlorobenzene-related

carcinogenic effects were not observed in female rats or mice of both sexes in the NTP bioassay (1985). In addition, liver carcinomas were observed in vehicle-treated male rats (2/50) but not in chlorobenzene-treated rats. Overall, the NTP bioassay on chlorobenzene provided some but not clear evidence of carcinogenicity. Therefore, chlorobenzene is classified as a U.S. EPA Group D carcinogen based on inadequate animal weight-of-evidence and the lack of human evidence.

6.3.2. Inhalation. No reports of carcinogenicity in humans or animals that were associated with inhalation exposure to chlorobenzene could be located in the available literature; hence, no estimation of carcinogenic potency has been made.

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APPENDIX

Summary Table for Chlorobenzene

	Species	Experimental Dose/Exposure	Effect	Reference Dose (RfD or RfD_S) (mg/day)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	rat	46 mg/kg/day	Focal lesions in liver, kidney tubules; hepatic and renal congestion; decreased SGOT	3	Dilley, 1977
RfD_I (formerly AIC)	rat	46 mg/kg/day	Focal lesions in liver, kidney tubules; hepatic and renal congestion; decreased SGOT	0.3	Dilley, 1977
Oral					
RfD_{SO}	dog	27.3 mg/kg/day for 90 days	None	14	Monsanto Company, 1967a
RfD_O	dog	27.3 mg/kg/day for 90 days	None	1.4	Monsanto Company, 1967a
Maximum composite score	dog	55 mg/kg/day for 90 days (RV_d = 2.0)	Immature leukocytes, conjunctivitis, vomiting and diarrhea (RV_e=4)	8	Monsanto Company, 1967a